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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/695,578	10/27/2003	Scott A. Waldman	100051.10611	5382

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EXAMINER	
AEDER, SEAN E	
ART UNIT	PAPER NUMBER
1642	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/695,578	WALDMAN, SCOTT A.	
	Examiner	Art Unit	
	SEAN E. AEDER	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

The Amendments and Remarks filed 11/11/08 in response to the Office Action of 7/10/08 are acknowledged and have been entered.

Claims 24-56 are pending.

Claims 27-29, 37-39, 47, and 52 have been amended by Applicant.

Claims 24-56 are currently under examination.

Response to Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24-56 remain rejected under 35 U.S.C. 112, first paragraph, for failing to comply with the enablement requirement for the reasons stated in the Office Action of 7/10/08 and for the reasons set-forth below.

The specification, while being enabling for methods for treating individuals who have metastasized colorectal cancer or who have been identified as being susceptible to metastasized colorectal cancer comprising administering a therapeutically effective or prophylactically effective amount of an expression vector comprising a nucleic acid sequence encoding amino acids 24-454 as set-forth in SEQ ID NO:2, **the specification does not reasonably provide enablement for** methods for treating individuals who have metastasized colorectal cancer or who have been identified as being susceptible

to metastasized colorectal cancer comprising administering a therapeutically effective or prophylactically effective amount of just any composition comprising a nucleic acid molecule that encodes just any epitope of human guanylyl cyclase C protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The instant claims are broadly drawn to methods for treating individuals who have metastasized colorectal cancer or who have been identified as being susceptible to metastasized colorectal cancer comprising administering a therapeutically effective or prophylactically effective amount of just any composition comprising a nucleic acid molecule that encodes just any epitope of just any human guanylyl cyclase C protein. This includes methods wherein nucleic acids are administered in compositions that would not generate polypeptides and would not produce a therapeutic or prophylactic response. Further, this is drawn to methods wherein nucleic acids comprising just any human guanylyl cyclase C protein epitope, including nucleic acids consisting of

transmembrane epitopes or nucleic acids consisting of cytoplasmic epitopes, are administered. Further, this is drawn to methods wherein nucleic acids comprising just any epitope of any receptor found on colorectal cells which binds to ST are administered.

The specification prophetically describes methods of treating an individual who has metastasized colorectal cancer or an individual who is susceptible to metastasized colorectal cancer with a vaccine comprising a nucleic acid molecule encoding at least one epitope of human ST receptor protein (page 11-12, in particular).

Further, the specification discloses the terms "ST receptor" and "guanylin cyclase C" are interchangeable and are broadly meant to refer to receptors found on colorectal cancer cells which bind to ST (see page 7). Further, the specification discloses the polypeptide set-forth as SEQ ID NO:2 is an ST receptor (see page 13). The specification further discloses that the extracellular region of SEQ ID NO:2 is from about amino acid 24 to about amino acid 454 of SEQ ID NO:2 (page 13). The specification further discloses that the transmembrane region of SEQ ID NO:2 is from about amino acid 455 to about amino acid 475 of SEQ ID NO:2 (page 13). The specification further discloses the cytoplasmic region of SEQ ID NO:2 is from about amino acid 476 to about amino acid 1093 of SEQ ID NO:2 (page 13).

It is further noted that the Reply of 5/2/08 states that "guanylyl cyclase C" is misspelled in the instant specification as "guanylin cyclase C". It is further noted that the specification does not limit the term "guanylyl cyclase C" (disclosed as "guanylin

cyclase C") to a particular SEQ ID NO. Rather, at lines 17-20 on page 7, the specification provides the following broad definition:

> "As used herein, the term "ST receptor" and "guanylin cyclase C" are interchangeable and meant to refer to the receptors found on colorectal cells, including local and metastasized colorectal cancer cells, which bind to ST."

Said definition is used to define the meaning of "guanylyl cyclase C" in the claims, as Applicant is entitled to be his or her own lexicographer (see MPEP 211.02). Therefore, the term "guanylyl cyclase C" is interpreted to encompass a genus comprising ALL receptors found on colorectal cells which bind to ST.

The Declaration of Scott Waldman demonstrates methods for treating individuals who have metastasized colorectal cancer or who have been identified as being susceptible to metastasized colorectal cancer comprising administering a therapeutically effective or prophylactically effective amount of a viral vector comprising a nucleic acid sequence encoding the first 430 amino acids of a guanylyl cyclase C protein. Said first 430 amino acids comprise extracellular binding domain regions of a guanylyl cyclase C. It appears SEQ ID NO:2 is a guanylyl cyclase C protein. The Declaration further describes a study wherein said guanylyl cyclase C protein is taught to be expressed on colorectal tumor cells and is an ideal target for immunotherapy. However, the Declaration does not address whether just any receptors found on colorectal cells which bind to ST would be ideal targets for immunotherapy. Further, the declaration does not demonstrate that the claimed invention would function in the absence of an expression vector, as contemplated by the specification.

As the claimed method is proposed to function as an immunotherapeutic method,

one of skill in the art would recognize that the administered nucleic acids must be translated into polypeptides like those found on the extracellular region of colorectal tumor cells in order to generate antibodies that recognize said colorectal tumor cells. Therefore, said nucleic acids must be administered in some kind of expression vector that delivers said nucleic acids into cells, where the nucleic acids can be translated. While the instant specification discloses that naked DNA vaccines are contemplated, such vaccines are highly unpredictable. For instance, Verma et al. (*Nature* 1997, 389: 239-242) teaches that the Achilles heel of gene therapy is gene delivery. Verma et al. state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression. Similarly, Amalfitano et al. (*Current Gene Therapy* 2002, 2: 111-133) teaches that non-viral mediated transfer of DNA generally suffers from low transduction efficiencies that would preclude therapeutic benefit.

Further, those of ordinary skill in the art recognize that treatment in vivo is not predictive. The instant situation is analogous to that of *In re* Brana (34 U.S.P.Q. 2d 1436, 1440 (Fed. Cir. 1995)). A review of *In re Brana* reveals an application that claimed a chemical compound for treating a cancer, wherein the chemical compound was structurally similar to known compounds that have known in vivo use to treat tumors, and more importantly, Applicant provided in vivo data that the claimed compound could treat tumors in mice, hence it was ruled that the claimed compound was enabled for treating tumors. In the instant application, nucleic acids of the instant methods administered in compositions that would not generate polypeptides, such as compositions lacking a viral vector comprising the nucleic acids, are not known in vivo

to give rise to a therapeutic effect. Further, nucleic acids consisting of sequences encoding polypeptides consisting of transmembrane or consisting of cytoplasmic regions of SEQ ID NO:2 are not known to give rise to a therapeutic effect in vivo. Further, nucleic acids encoding just any receptor found on colorectal cells which binds to ST are not known in vivo to give rise to a therapeutic effect. In view of *In re Brana*, Examiner asserts that successful use of in vivo mouse models of colon cancer enables compositions for specific therapeutic effects in humans and does not require human clinical testing.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to methods for treating individuals who have metastasized colorectal cancer or who have been identified as being susceptible to metastasized colorectal cancer comprising administering a therapeutically effective or prophylactically effective amount of just any composition comprising a nucleic acid molecule that encodes just any epitope of just any protein that binds ST on colorectal cancer cells, and Applicant has not enabled said method because it has not been shown that administering just any composition comprising a nucleic acid molecule that encodes just any epitope of just any protein that binds ST on colorectal cancer cells would predictably treat individuals who have metastasized colorectal cancer or who have been identified as being susceptible to metastasized colorectal cancer.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of

skill in the art to determine with any predictability, that the method would function as broadly claimed.

In the Reply of 11/11/08, Applicant argues that working examples are not required. Applicant further argues that the Office has failed to put forward any reasonable evidence in view of the specification and the declaration that raises doubt as to the enablement of the pending claims. Applicant further argues that the disclosure and the data provided in the Waldman declaration make clear that the claimed invention is operable in vivo. Applicant further argues that Verma et al and Amalfitano are unrelated to the claimed invention because they refer to gene therapy wherein persistent gene expression over a long period of time is desired and the instant claims are not directed to methods wherein one needs persistent gene expression.

The amendments to the claims and the arguments found in the Reply of 11/11/08 have been carefully considered, but are not deemed persuasive. In regards to the argument that working examples are not required, working examples are a way of demonstrating predictability in an unpredictable art such as cancer therapeutics. As discussed above, predictability is a factor in determining enablement. Further, this invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology". Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

In regards to the argument that the Office has failed to put forward any reasonable evidence in view of the specification and the declaration that raises doubt as to the enablement of the pending claims, teachings of Verma et al and Amalfitano

demonstrate the unpredictability of performing the claimed method without an expression vector. As the claimed method is proposed to function as an immunotherapeutic method, one of skill in the art would recognize that the administered nucleic acids must be translated into polypeptides like those found on the extracellular region of colorectal tumor cells in order to generate antibodies that recognize said colorectal tumor cells. Therefore, said nucleic acids must be administered in some kind of expression vector that delivers said nucleic acids into cells, where the nucleic acids can be translated. While the instant specification discloses that naked DNA vaccines are contemplated, such vaccines are highly unpredictable. For instance, Verma et al. (*Nature* 1997, 389: 239-242) teaches that the Achilles heel of gene therapy is gene delivery. Verma et al. state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression. Similarly, Amalfitano et al. (*Current Gene Therapy* 2002, 2: 111-133) teaches that non-viral mediated transfer of DNA generally suffers from low transduction efficiencies that would preclude therapeutic benefit. Further, those of ordinary skill in the art recognize that treatment in vivo is not predictive. The instant situation is analogous to that of *In re* Brana (34 U.S.P.Q. 2d 1436, 1440 (Fed. Cir. 1995)). A review of *In re Brana* reveals an application that claimed a chemical compound for treating a cancer, wherein the chemical compound was structurally similar to known compounds that have known in vivo use to treat tumors, and more importantly, Applicant provided in vivo data that the claimed compound could treat tumors in mice, hence it was ruled that the claimed compound was enabled for treating tumors. In the instant application, nucleic acids of the instant

methods administered in compositions that would not generate polypeptides, such as compositions lacking a viral vector comprising the nucleic acids, are not known in vivo to give rise to a therapeutic effect. Further, nucleic acids consisting of sequences encoding polypeptides consisting of transmembrane or consisting of cytoplasmic regions of SEQ ID NO:2 are not known to give rise to a therapeutic effect in vivo. Further, nucleic acids encoding just any receptor found on colorectal cells which binds to ST are not known in vivo to give rise to a therapeutic effect. In view of *In re Brana*, Examiner asserts that successful use of in vivo mouse models of colon cancer enables compositions for specific therapeutic effects in humans and does not require human clinical testing.

In regards to the argument that the disclosure and the data provided in the Waldman declaration make clear that the claimed invention is operable in vivo, the disclosure and the data provided in the Waldman declaration do not make clear that the claimed invention is operable *in commensurate with the scope of the claims*. The disclosure and the data provided in the Waldman declaration demonstrate methods for treating individuals who have metastasized colorectal cancer or who have been identified as being susceptible to metastasized colorectal cancer comprising administering a therapeutically effective or prophylactically effective amount of an expression vector comprising a nucleic acid sequence encoding amino acids 24-454 as set-forth in SEQ ID NO:2. However, the disclosure and the data provided in the Waldman declaration do not make clear that an individual would successfully be treated with naked DNA encoding just any epitope of just any receptor of ST on colorectal

cancer cells, as encompassed by the claims. Again, it is noted that the term "human guanylyl cyclase C protein" is not limited to definitions of "human guanylyl cyclase C protein" found in the art or in the Waldman Declaration; rather, "human guanylyl cyclase C protein" encompasses just any receptor of ST on colorectal cancer cells.

In regards to the argument that Verma et al and Amalfitano are unrelated to the claimed invention because they refer to gene therapy wherein persistent gene expression over a long period of time is desired and the instant claims are not directed to methods wherein one needs persistent gene expression, Verma et al and Amalfitano are cited because they provide evidence that contemplated naked DNA vaccines would be highly unpredictable. Verma et al. (*Nature* 1997, 389: 239-242) teaches that the Achilles heel of gene therapy is gene delivery. Verma et al. state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression. Without expression, the instant invention would not predictably function. Similarly, Amalfitano et al. (*Current Gene Therapy* 2002, 2: 111-133) teaches that non-viral mediated transfer of DNA generally suffers from low transduction efficiencies that would preclude therapeutic benefit. While the examples in the Waldman Declaration use viral vectors, the instant claims do not require use of such vectors. Further, Applicant has not demonstrated the assertion that persistent gene expression is not required in the instant method.

Summary

No claim is allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SEAN E. AEDER whose telephone number is (571)272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sean E Aeder/
Examiner, Art Unit 1642